dpr

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DATE: May 25, 2007

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SUBJECT: **Endosulfan.** Department of Pesticide Regulation Response to USEPA's Review of California's Endosulfan Risk Characterization Document

This document "*Department of Pesticide Regulation Response to USEPA's Review of California' s Endosulfan Risk Characterization Document*" was generated to respond to the January 31, 2007 comments by USEPA on the draft risk assessment document of December 5, 2006.

Toxicology:

USEPA COMMENT: A comparison of the risk assessments produced by CDPR in 2006 and the Agency in 2002 and currently in 2007 reveals two major differences in hazard assessment. The first difference is the lack of the use of the DNT study (Gilmore, 2006; MRID 46968301) in risk assessment by CDPR. The Agency is currently planning to use the DNT study for the dermal short- and intermediate-term scenarios.

DPR RESPONSE: USEPA selected a dermal NOEL of 1.2 mg/kg/day for short term (1-30 days) and intermediate term (1-6 months) from "co-critical studies"; the rat reproduction study, based on decreased body weight (NOEL = 1.18 mg/kg/day, Edwards et al., 1984) and the DNT study, based on decreased pup weight (LOAEL = 3.74 mg/kg/day—no NOEL established according to their review; Gilmore, 2006). This information, obtained from Table 1 in the USEPA MEMORANDUM, was added to the DPR RCD. In contrast, DPR did not establish a subchronic dermal endpoint, since there were no FIFRA Guideline acceptable studies. Instead

DPR used the subchronic oral NOEL from the rat reproduction study (1.18 mg/kg/day; dermal penetration factor of 47.3%), since this was a lower NOEL than DPR identified for the DNT study and it was also an acceptable FIFRA Guideline study.

USEPA COMMENT: Furthermore, the established endpoints of the DNT study by CDPR differ from the identified endpoints by the Agency and are described briefly below.
DNT- (Gilmore et al., 2006; MRID 46968301)
The Agency recently received a developmental neurotoxicity study with endosulfan in Wistar rats in December 2006. The study was reviewed and the findings then presented to the Developmental Neurotoxicity Committee on January 10, 2007. Based on the review of the study by the DNT Committee, the Committee concluded that there was no NOAEL for pups. The LOAEL of 3.74 mg/kg/day was the lowest dose tested (LDT), based on decreased pup weight [PND 11] and weight gain [PND 4-11], with delayed preputial separation in males receiving the MDT. For dams, the NOAEL is 3.74 mg/kg/day. The LOAEL for dams is 10.8 mg/kg/day, based on decreased body weight, food consumption and food efficiency. This study is acceptable/guideline. The data evaluation record (DER) is currently being revised to reflect changes requested by the DNT Committee.

DPR RESPONSE: The maternal NOEL was less than 3.74 mg/kg/day, based upon lower mean body weights (5 - 6%) and lower food consumption (12%) at 3.74 mg/kg/day. While these decreases are marginal, the trend is dose-related and therefore DPR chose to note it as a treatment-related effect. The developmental NOEL was less than 3.74 mg/kg/day based upon the lower mean body weights (8% on post-partum day 11 only) of the offspring at 50 ppm. USEPA pointed out that there was also a decreased body weight gain in pups that was noted on post-partum day 11 only. It was therefore considered by DPR to be a transitional effect, but it will be noted in the DPR RCD

USEPA COMMENT: The second difference among the risk assessments is the critical study identified for the acute dietary assessment. CDPR used the developmental rabbit study (MRID 00094837) NOEL of 0.7 mg/kg/day, based on convulsions that were considered acute effects by CDPR. The Agency, however, established the salivation, convulsions, rapid breathing, and hyperactivity observed at 1.8 mg/kg/day to only occur on day 10 of gestation (not gestation day 6 as indicated by CDPR). Therefore the Agency relied on the acute neurotoxicity study (MRID 44403101) NOAEL of 1.5 mg/kg/day since convulsions were observed 8 hours after a single oral dose, thus making the endpoint more appropriate for the acute dietary assessment.

DPR RESPONSE: The acute oral effects observed in a developmental toxicity study performed in the rabbit, included maternal signs within the first day of treatment (in the absence of fetal effects). Various clinical signs were observed in dams/does, including abortions, phonation, coughing, cyanosis, convulsions/ thrashing, noisy/rapid breathing, hyperactivity, salivation, and nasal discharge and death (Nye, 1981). Clinical signs began on gestation day 6 (day 1 of treatment) at 1.8 mg/kg/day. In particular, hyperactivity was observed only at 1.8 mg/kg/day (no convulsions; thrashing, phonation, coughing, and cyanotic only; page 14 of the report by Nye, 1981). The NOEL for this study was 0.7 mg/kg/day. Similar effects were observed in 2 rangefinding studies also performed in pregnant New Zealand rabbits (Fung, 1981a, b). In these studies the LOELs were 1.0 mg/kg/day, based on neurotoxicity and deaths beginning day 8 of gestation (treatment day 2). There were no major deficiencies in the rabbit developmental study and it provided the lowest acute oral NOEL. The other studies described above, showed that female rats are more sensitive to acute oral endosulfan treatment than are males and that pregnant female rabbits are more sensitive to endosulfan than are both non-pregnant and pregnant rats. Although the rabbit developmental study involved multiple dosing, rather than a single acute oral dose of endosulfan, the neurotoxic effects were seen on the first day of treatment and were therefore acute oral effects. Therefore, this study, with a critical NOEL of 0.7 mg/kg, was selected as the definitive study for evaluating acute dietary exposure and to calculate the MOE for potential acute single-day (non-inhalation) human exposures to endosulfan.

DPR made no changes to Table 43 in the RCD. It remains as viewed by USEPA prior to your response, with data from the RED, 2002. It has been noted in the RCD that certain endpoints and FQPA factors are under reevaluation by USEPA and that DPR will update the RCD when the data are received.

Dietary Assessment

USEPA CONCERNS AND COMMENTS: HED has the following comments on the dietary portion of the CDPR endosulfan characterization document. It is important to note that the original CDPR dietary assessment is from 1998. There is an addendum dated September 2006 that addresses the need for a complete revision of the 1998 dietary assessment. A complete reassessment was not conducted. Comparisons will be made between the 1998 CDPR assessment (and addendum) and the 2002 HED dietary assessment. The 2002 HED dietary assessment is likely to change in the near future based upon review of additional submitted data.

HED does not usually present screening level assessments if a more refined assessment has been done. HED only presents the more refined assessment. The CDPR assessment includes data that has been refined (with percent crop treated and PDP monitoring data) as well as a general screening assessment assuming 100% crop treated and tolerance level residues.

Neither assessment included consumption data for drinking water.

The CDPR assessment discusses populations upon which HED does not normally base regulatory decisions on.

The CDPR assessment discusses acute exposures at the 95th percentile. HED typically bases regulatory decisions on the 99.9th percentile.

The CDPR dietary assessment from 1998 used the TAS, Inc EX™ acute and chronic dietary exposure software (TAS, 1996). The 2002 HED dietary exposure assessment used the DEEM™ dietary exposure model. The dietary modeling software program is important to determine if the recipes and age groupings are the same as those used by HED. In other words, an assessment done with a program other than DEEM cannot be directly compared to an assessment done with DEEM. The results could vary based upon this fact. Both HED and CDPR now use the DEEM-

FCID™ modeling software. Also, the DEEM™ food recipe libraries may well differ from those used by the TAS, Inc EX™ software.

The TAS, Inc EX™ acute and chronic dietary exposure software analyzes acute exposure, seasonal exposure for California workers, chronic exposure (1 year), and lifetime exposure (oncogenic). Since DPR had no oncogenic exposure factor for endosulfan, a lifetime dietary exposure was not performed. HED conducts acute and chronic (lifetime - age 0 to 85 years) dietary exposure assessments.

The CDPR assessment and the most recent HED risk assessment completed (Endosulfan RED, 2002) both used the same Continuing Survey of Food Intake by Individuals (CSFII) consumption database from 1989-1992. There is a newer database that is currently in use by both HED and DPR (CSFII 1994-1996 and 1998). This newer consumption database will be used in the event the upcoming HED endosulfan risk assessment conducts quantitative dietary risk calculations.

The CDPR assessment used residue data from the following sources: DPR monitoring program (1993-1995), registrant field residue trials, USDA 1994 or 1996 PDP monitoring program, or USDA 1995 FSIS residue monitoring program. A US EPA tolerance level was only used as the exposure value for sugarcane and its processed commodities. The 2002 HED assessment used a combination of data from PDP, FDA, and registrant field trials. HED typically uses the most recent 5 years of monitoring data and the assessments are supposed to be updated using anticipated residues every 5 years.

For the reasons listed in the draft document, HED agrees with the CDPR conclusion regarding the 2006 dietary addendum being sufficient when combined with the prior 1998 DPR dietary exposure assessment. With the nine tolerances canceled or proposed for cancellation by the registrant and 5 tolerances revoked by the Agency (72 uses decreased to 58), decreased maximum application rates for a number of commodities, along with the fact that the FQPA safety factor is likely to be reduced, it is highly unlikely that dietary risks will exceed the Agency's level of concern. This same rationale will likely be used in conducting the forthcoming 2007 HED dietary risk assessment.

DPR RESPONSE: The USEPA dietary exposure comments are part of the memo from Dr. D. Wilbur et al. to Dr. T. Perry dated January 31, 2007 (USEPA, 2007).

The memo did not contain any comments that require a DPR response. The dietary exposure section of the DPR draft endosulfan RCD is addressed on page 9 of the 16 page USEPA memo. Specifically, the memo agrees with the conclusion of the DPR RCD that the DPR dietary exposure addendum (dated September 29, 2006) combined with the 1998 DPR assessment are sufficient to address dietary exposure concerns. Therefore, an updated DPR dietary exposure assessment is unnecessary. DPR concurs with the U.S. EPA statement.

USEPA COMMENT: HED used an acute endpoint of 1.5 mg/kg/day (with an uncertainty factor of 100 and a FQPA safety factor of 10) and a chronic endpoint of 0.6 mg/kg/day (with an uncertainty factor of 100 and a FQPA safety factor of 10). CDPR used an acute endpoint of 0.7 mg/kg/day and a 0.57 mg/kg/day chronic endpoint. There is also mention of a NOEL of 0.25

mg/kg/day used as a chronic endpoint. This is referred to in Appendix A (original 1996 dietary assessment). [page 8 of 16 of Memorandum]

DPR RESPONSE: The NOEL for the chronic dog study mentioned in the Appendix A (original 1998 dietary assessment) was an error and was corrected to 0.57.

NOTE: A response to the comments on Occupational/Residential Assessment is being prepared by the Worker Health and Safety Branch as a separate document.

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SUBJECT: DPR RESPONSE TO THE OEHHA COMMENTS AND RECOMMENDATIONS REGARDING THE DRAFT RISK CHARACTERIZATION DOCUMENT FOR ENDOSULFAN

Thank you for your helpful comments. They were thorough and we believe they have greatly improved the document. Following below are the responses to the OEHHA recommendations.

Major Comments

Major Comment #1: OEHHA disagrees with the RCD's use of oral studies to evaluate inhalation exposures. In Tables 35-38, margins of exposure (MOEs) are calculated for persons exposed to endosulfan via the inhalation route. The inhalation MOEs are calculated using no-observed-effects-levels (NOELs) from studies in which the animals were exposed to endosulfan via the oral/dietary route. However, Table 11 shows that rats exposed subchronically to endosulfan were significantly more sensitive via the inhalation route compared to the dietary route: 10-fold more sensitive comparing the subchronic inhalation NOEL to the subchronic dietary NOEL, and 6-fold more sensitive comparing the subchronic inhalation NOEL to the week 24 parental NOEL determined in the two-generation dietary study. For both of these comparisons, the inhalation lowest-observed-effects-level (LOEL) was lower than the corresponding oral NOEL (Table 11), demonstrating that differences in dose selection were not responsible for the apparently greater sensitivity of the inhalation route. Therefore, OEHHA recommends using the subchronic inhalation study in the rat (Hollander et al., 1984) to evaluate subchronic/seasonal inhalation exposures to endosulfan. This study conformed to Federal

Insecticide, Fungicide, and Rodenticide Act guidelines, and was designated “acceptable” by reviewers from both U.S. EPA and DPR.

Since an “acceptable” subchronic inhalation study is available, OEHHA recommends it be used to calculate all subchronic inhalation MOEs. The draft RCD calculates subchronic inhalation MOEs for members of the general public in Table 38 using this inhalation study. However, an oral study is used for calculating subchronic inhalation MOEs for workers (changed to Tables 36, 37 and 38). Unless justification can be provided, OEHHA recommends that this apparent inconsistency be corrected by applying the same subchronic inhalation study by Hollander et al. (1984) to subchronic inhalation MOE calculations for both workers and members of the general public.

Since no acceptable acute or chronic inhalation studies are available, a decision is required as to what study should be used to calculate inhalation MOEs for those exposure periods. Looking at the oral NOELs from the rat studies presented in Tables 10-12 (now Tables 11-13) of the RCD, they were 2.0, 1.18 and 0.6 mg/kg-day for the developmental (acute), subchronic and chronic studies, respectively. This is a relatively narrow range for acute through chronic dosing in the same species via the oral route. A similar narrow range may exist for exposures via the inhalation route. Therefore, OEHHA recommends using the subchronic inhalation NOEL, possibly with an adjustment factor, for calculating all (acute, subchronic/seasonal and chronic) inhalation MOEs.

DPR RESPONSE: DPR agrees and the subchronic inhalation study with a NOEL of 0.194 mg/kg/day was used for relevant acute and subchronic occupational exposures and MOEs and for acute and subchronic ambient air and bystander exposure scenarios. For chronic inhalation exposures and MOEs, a 10x adjustment was used to extrapolate from subchronic to chronic (ENEL = 0.0194 mg/kg/day). These new estimations are presented in corresponding tables in the RCD. For the combined exposures and combined MOEs, however, the occupational total (dermal + inhalation) exposures in combination with the dietary exposures were used with the oral NOELs (except in the case of the ambient air and bystander MOEs).

Major Comment #2: OEHHA recommends using the most recent pesticide residue and food consumption data sets to estimate dietary exposures to endosulfan. Some raw agricultural commodities (RACs) measured in the more recent residue monitoring program (United States Department of Agriculture Pesticide Data Program, 1994 for broccoli only and 1997-2004 annual summaries) exhibited increased endosulfan residue concentrations (Now Table 25, formerly Table 24) compared to the older residue data used in the RCD’s exposure assessment (DPR 1993-1995 market basket program). In addition, the per person consumption rates of some RACs treated with endosulfan were higher in the more recent Continuing Survey of Food Intake by Individuals (1994-98 CSFII) compared to the older food consumption data set used in the RCD’s dietary exposure assessment (1989-92 CSFII). Thus, it is possible that some dietary exposures to endosulfan, calculated using the newer data sets, would be higher than the exposures calculated in the RCD. Therefore, OEHHA recommends doing the dietary exposure assessment with the two more recent data sets. Given some of the low acute dietary margins of exposure (MOEs) for some of the population subgroups shown in Table 40 (changed to Table 41), this seems the prudent thing to do.

DPR RESPONSE: The comment at the top of page 3, first paragraph, regarded the need to redo the DPR dietary exposure assessment. The DPR dietary exposure assessment resulted in acute and chronic MOEs that were more than sufficient when originally conducted. The MOEs were greater than 100 for all population subgroups using pesticide use rates and existing endosulfan tolerances in effect during 1998. The 1998 DPR dietary exposure assessment combined with the information in the DPR dietary exposure addendum suggest that additional refinement is unnecessary (Carr, 1998, 2006). In particular, the DPR addendum was written to indicate why the original 1998 assessment is still acceptable. The addendum summarized the label reductions and tolerance cancellations proposed in the draft U.S. EPA 2002 endosulfan RED, similarities between the 1989-92 and 1994-98 CSFII consumption databases and differences between the USDA-PDP and DPR residue programs. Since the acute and chronic MOEs from the 1998 DPR assessment are adequate, the DPR concluded that updating the endosulfan dietary exposure assessment would not likely result in MOEs of 100 or lower. To the contrary, based on data summarized in the DPR addendum, it is likely the MOEs would improve if the dietary exposure assessment were to be updated. Therefore, it was determined that this would not be an effective use of limited DPR staff resources. The U.S. EPA reviewed the DPR draft endosulfan RCD and reached a similar conclusion regarding the sufficiency of the dietary exposure assessment (Silva, 2006; U.S. EPA, 2007).

Major Comment #3: On pages 47-48 the RCD discusses endocrine effects of endosulfan in young rats. Two studies detected effects on male reproductive endpoints at low dose levels: decreased spermatid counts, decreased sperm counts and sperm abnormalities at 2.5 mg/kg-day in 3 week-old animals (Sinha et al., 1997), as well as decreased weight of testes, epididymis, ventral prostate and seminal vesicle at 1.0 mg/kg-day in 6 week-old animals (Chitra et al., 1999). The latter value of 1.0 mg/kg-day is lower than the LOELs of all critical studies selected for calculating oral MOEs (Tables 10-12, changed to Tables 11-13). OEHHA recommends discussing the reasons these effects on male reproductive organs/function were not chosen as the critical effects for risk assessment.

DPR RESPONSE: The following information was added to the RCD (page 168).

Many recent studies with neonatal or prepubescent male animals and pubescent human males have implicated endosulfan with effects on the development of the reproductive tract or sperm (Ahmad et al., 1993, Dalsenter, et al., 1999, 2003; Saiyed et al., 2003). Prepubescent male rats were susceptible to effects of endosulfan on reproductive organs following repeated dosing, while humans (Saiyed et al., 2003) showed effects to testosterone and LH. The main problem with the open literature studies, however, is that clinical signs were either not reported or not measured. Therefore, it is not known at what doses effects to the reproductive tract occur, compared to doses that induce neurotoxicity.

With regard to the Saiyed, et al., 2003 study, the only thing that can be concluded is that the children exposed to endosulfan had a higher blood level of endosulfan (1.37 ± 0.23 ppb, control; 7.47 ± 1.19 ppm, exposed). Sexual maturation appeared to be delayed; however, the authors state the weakness in the study are 1) non-participation in the SMR (57% of the exposed and 33% of the control participants did not agree to undergo SMR examination). 2)

Blood was collected only once from participants and sex hormone levels can vary depending on individual variation and time of day (personal cycle). The random variability of the sex hormone levels was stated to weaken the power of the study. The authors conclude that a study with a larger sample size must be performed and that a long-term follow up must be done on individuals in order to understand the implications or suggestions initially identified. Further criticism was published in "Perspectives – Correspondence: Endosulfan's Effects: Omissions and Flawed Data" (Abraham, C.C.) and "Endosulfan's Effects: Inaccurate Data," (Indulkar, A.S.) along with "Endosulfan's Effects: Saiyed's Response," (Saiyed, H.N.); Environmental Health Perspectives, 112(10): A538 – A541, 2004. Information presented in this paper yields at best a suggestion of an effect by endosulfan, however this paper cannot be used as a strong basis for effects in humans.

Zaidi et al. (1985) showed rat pups receiving endosulfan had increased ^{3}H-serotonin binding to frontal cortical membranes that correlated with increased foot-shock induced fighting behavior at 1.0 mg/kg/day (adult rats were affected, with less sensitivity at 3.0 mg/kg/day). This indicates a greater sensitivity in neonatal animals than adults. Studies with neonatal (3 week old) rats showed decreased intratesticular sperm counts and increased percentage of abnormal sperm at lower doses than observed in 3-month-old adults (Sinha et al., 1995 and 1997).

The study by Chitra et al. (1999) treated Wistar male prepubertal (45 day old) rats by gavage with endosulfan technical at 1.0 mg/kg/day (6 animals) for 30 days (Chitra, et al., 1999). While results at termination showed statistically significant effects in reproduction parameters (decreased testes, epididymal, ventral prostate, and seminal vesicle weights) and effects to 3-βOH-steroid dehydrogenase among other biochemical parameters relating to testicular metabolism. These findings suggest a possible connection between endosulfan treatment and steroidogenesis inhibition in male rats. However, there were major deficiencies in this study (only 6 animals treated, only a single dose, no individual data were shown, and there was a great deal of variation in assay results) that prevent its use as a critical endpoint study. More recent studies, such as the developmental neurotoxicity study reported in 2006 (Gilmore et al.) that is an acceptable FIFRA Guideline study, provide more reliable data for regulatory purposes.

Minor Comments

OEHHA COMMENT: Page two, third paragraph. Recommend explaining what a "centrally acting agent" is.

DPR RESPONSE: This sentence now reads: There is a concern about hazards caused by the interaction of endosulfan and therapeutic agents that act on the central nervous system, since endosulfan is a potent MFO inducer.

OEHHA COMMENT: Page four, second paragraph. "Of the 55 illnesses resulting from exposure to endosulfan in combination with other pesticides, 42 occurred as the result of exposure to residue, …" Recommend clarifying whether these were field residues, or some other type of residue.

WH & S RESPONSE: The word "field" was inadvertently omitted. I've added it ("field residues on treated crops"). Also, addition of the 2004 PISP data added a single illness, also in a fieldworker exposed to field residues. The first 3 paragraphs of the Reported Illnesses currently read as follows (note changes in some of the numbers):

Reports of illness and injury with definite, probable, or possible exposure to pesticide products are recorded in a database maintained by the Pesticide Illness Surveillance Program (PISP) at DPR. The PISP database contains information about the nature of the pesticide exposure and the subsequent illness or injury. In California between 1992 and 2004, 63 illnesses were reported to the Pesticide Illness Surveillance Program that suggested the involvement of endosulfan, alone or in combination with other pesticides (Verder-Carlos, 2006). Of the 63 illnesses, 61 resulted from agricultural applications and just two from non-agricultural applications. Five agriculturally-related and both of the non-agriculturally-related illnesses and injuries were attributed solely to endosulfan; the other 56 reports were associated with endosulfan in combination with other pesticides.

Of the seven illnesses and injuries attributed solely to endosulfan, one occurred as the result of exposure to field residues, three resulted from handling processes (mix/load, apply), two resulted from drift, and one followed a non-specified exposure. Of the 56 illnesses resulting from exposure to endosulfan in combination with other pesticides, 43 occurred as the result of exposure to field residues on treated crops, six occurred during the application process (mix/load, apply, flag), and seven occurred as the result of drift exposure.

Table 2 summarizes types of symptoms reported in association with endosulfan exposure. The majority of illnesses involved skin and eye effects, such as irritation and rashes. Several incidents involved more than one worker. None of the incidents resulting in multiple exposure involved endosulfan as the only pesticide. Of the 44 field worker illnesses and injuries, 31 (70%) harvesting cucurbits (melons, cucumbers), and seven (16%) occurred while working in grapes. The remaining six (14%) occurred in various other crops.

The illness summary table also gets an addition, into the "Skin" column, which has 23 reports associated with endosulfan with other pesticides, for a total of 24. The last column totals are now 7, 56, and 63.

OEHHA COMMENT: Page four, last paragraph. If available, recommend stating the length of exposure rather than “prolonged.”

WH & S RESPONSE: The paragraph is changed as follows:

In the southeastern U.S., two incidents were reported in which mixer/loader/applicators (M/L/As) pouring endosulfan without proper protective equipment experienced serious illnesses (Brandt et al., 2001). In both cases, endosulfan splashed onto skin and clothing during mixing and loading; in the second case, drift during the application, enough that his clothes “appeared soaked,” was witnessed. Both individuals proceeded with the applications without washing skin or changing the contaminated clothing. Exposure durations were estimated at 4 -

5 hours. Evidence suggested that these exposures resulted in long-term neurological damage in one case, and in death in the other case.

OEHHA COMMENT: Page nine, last paragraph. Where it is stated that, "no endosulfan residues have been detected in drinking water in California in the past three years for which data are available," recommend adding the approximate (or exact) number of samples upon which this statement is based.

DPR RESPONSE: The comment at the top of page 4, first paragraph, regarding drinking water. DPR can provide the additional data. Three years of drinking water data from California were sampled by the USDA-PDP program between 2001-2003 (USDA, 2003, 2004, 2005). A total of 424 California water samples were analyzed with a limit of detection of 0.1 ppb or better. No endosulfan or endosulfan degradates were detected.

This information was added: California drinking water data (3 years) from between 2001-2003 were examined by the USDA-PDP (USDA, 2003, 2004, 2005). A total of 424 California water samples were analyzed with a limit of detection of 0.1 ppb or better. No endosulfan or endosulfan degradates were detected. The number of samples by year were: 2001; 144, 2002; 140, and 2003; 140. The samples were collected from municipal water processing facilities post-processing and ready to drink. These results suggest that drinking water systems in California are not likely to be a source of human exposure to endosulfan.

OEHHA COMMENT: Page 11, second paragraph. "In California, endosulfan has been monitored and detected in 34/39 or 23/39 samples by 8 hours after application for the alpha- and beta-isomers, respectively." Recommend adding where this air sampling was performed. For example, were these samples taken in the fields, or in towns miles away from the fields?

DPR RESPONSE: See Appendix A, Table 14 for a summary of endosulfan concentrations and locations of monitoring stations; Beauvais, 2007.

OEHHA COMMENT: Page 12, last paragraph. Recommend explaining what is meant by endosulfan being bioconcentrated 5.2 times but having a bioconcentration factor of 37.5 (for example).

DPR RESPONSE: The paragraph has been changed to the following:

Endosulfan is also bioconcentrated in 2 strains of fish (*Labeo rohita* & *Channa punctata*) that were treated with α- and β-endosulfan at 0, 0.1414 and 0.2274 ug/l for one month (Ramaneswari and Rao, 2000). Tissue analyses showed that the isomers of endosulfan persisted in the fish. Both the α- and β-isomers were persistent in both strains of fish, with α-occurring at higher concentration. In *L. rohita*, the α- form was bioconcentrated 5.2 times and had a bioconcentration factor (relative uptake of endosulfan from it's medium by the organisms) of 37.5. The β-form was bioconcentrated 7.7, with a bioconcentration factor of 55.4. In *C. punctata*, the α- form bioconcentration was 1.8 times and had a bioconcentration factor of 13.2 and the β-form bioconcentration was 11.8, with a bioconcentration factor of 13.4.

Endosulfan sulfate was found as a metabolite in *L. rohita* only (bioconcentration = 0.54; no bioconcentration factors were reported).

OEHHA COMMENT: Page 16, third paragraph. It is not clear why the percent total absorption (47.3 percent) was calculated using the percent absorption at the two lowest dose levels, rather than just the percent absorption at the lowest dose level (the lowest dose level showed the greatest absorption at 24 hours). Since the value of 47.3 percent is used by the Worker Health and Safety Branch to calculate occupational exposures, we recommend this be explained.

WH & S RESPONSE: The mean 168-hour absorption of the two lowest doses was used, rather than the absorption of the lowest dose, because at 168 hours the greatest absorption was associated with the mid-level dose, not the lowest dose - but the percent absorption was nearly the same for both doses (see Table 6 in the EAD). Although greater penetration was documented in the lowest dose than in the other doses at 24 hours, at that point there were extensive bound skin residues. Had the 24-hour low-dose results been used, all of the bound skin residues would have been included in the absorbed dose estimate (because we anticipate that some portion would be absorbed), resulting in an estimated 63.5% dermal absorption value (22.1% penetrated + 41.4% bound to skin). As we have data at 7 days (168 hours) showing that the total residues that were penetrated and bound to skin is just under 50% (44.8% + 1.7% = 46.5%), using the 24-hour value would give an inappropriate overestimate of dermal absorption. To clarify in the EAD, the text before Table 6 was revised as follows:

Craine (1988) reported that amounts of ^{14}C-endosulfan recovered from the application site decreased over time, while amounts of residues in excreta increased. These trends suggest that residues bound to skin are bioavailable. For example, at 24 hrs in the low dose animals, the residues in the skin represented 41.4% of the applied dose; residues declined to 23.8% and 7.0%, respectively, at the 48-and 72-hr sacrifice time periods. Similar declines in bound skin residues occurred at the two higher treatment levels.

A portion of the bound skin residues recovered in any dermal absorption study are expected to be absorbed; as the amount that will be absorbed is unknown, standard practice is to include bound skin residues in estimates of absorbed dose (U.S. EPA, 1998c). The results from 168 hours post-dose suggest that much of the residues in the skin at 24 hours were not absorbed. Because of the large amount of residue bound to skin at 24 hours, dermal absorption can be more accurately estimated using data from 168 hours post-dose (Table 6). DPR selected the mean dermal penetration of the two lowest doses (47.3%) to estimate absorbed dosages, as the lowest doses approximate levels of endosulfan exposure experienced by handlers and fieldworkers. Total recoveries of administered doses averaged above 90%, precluding any need to adjust the estimated dermal absorption for absorbed dose recovery.

A new reference (U.S. EPA, 1998c) was added, cited in the newly added text:

U.S. EPA. 1998c. Health Effects Test Guidelines. Health Effects Test Guidelines: Dermal Penetration (OPPTS 870.7600). Washington, DC: Office of Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency.

http://www.epa.gov/opptsfrs/publications/OPPTS_Harmonized/870_Health_Effects_Test_Guidelines/Series/870-7600.pdf

OEHHA COMMENT: For Table 3, recommend specifying whether the values are means.

DPR RESPONSE: The correction was added ("means").

OEHHA COMMENT: On page 31 is a discussion of a rat subchronic dietary study. The text's characterization of the data in Table 3 contains a number of inaccuracies. Recommend correcting. In addition, there were decreases in red blood cells (RBCs) and hemoglobin at 1.92 mg/kg-day, and microscopic alterations to the kidneys at 0.64 and 1.92 mg/kg-day, which might be used to argue for a lower NOEL than that designated in the draft RCD for this study (1.92 mg/kg-day). Thus, the absence of these effects in the rat chronic dietary study (Table 5) is noteworthy. OEHHA recommends noting this in the discussion of the subchronic study.

DPR RESPONSE: The corrections were made in the discussion as follows:

Microscopically, livers showed granular brown pigment in males and centrilobular enlargement of hepatocytes at 23.41 mg/kg/day for males and 27.17 mg/kg/day for females. In kidneys, discoloration (pigmentation) was increased primarily at 3.85 mg/kg/day and greater in males and for females, 4.59 mg/kg/day and greater but it was reduced to trace amounts or was completely reversed after the 4-week recovery. Granular/clumped pigment remained in males after recovery. Both the discoloration and the granular/clumped pigments continued after treatment, it did not seem to have any toxicological effect.

RBCs were statistically significantly decreased in males (≥ 1.92 mg/kg/day, week 6; ≥ 3.85 mg/kg/day, week 13 and at 23.41 mg/kg/day week 17 recovery). In females RBCs were statistically significantly decreased (≥ 4.59 mg/kg/day, week 6; 27.17 mg/kg/day, week 13, reversed at week 17 recovery). In males hemoglobin (Hb) was statistically significantly decreased (≥ 1.92 mg/kg/day week 6; 23.41 mg/kg/day week 13; ≥ 3.85 mg/kg/day at recovery). In females Hb was decreased (≥ 4.59 mg/kg/day, week 6; ≥ 0.75 mg/kg/day—not dose related, week 13; reversed at recovery).

A note that these effects to RBCs, Hb, and kidney (granular/clumped pigments and discolored pigment) were not observed in the chronic rat study was added to the Hazard ID section.

OEHHA COMMENT: Page 33, bottom paragraph. It is mentioned that the animals exhibited hyperexcitability, tremor, dyspnea and salivation at all dose levels. However, the mid-dose level was chosen as the NOEL in both cases (male and female). Recommend explaining why the clinical signs at the lowest dose level were not used to set the LOEL.

DPR RESPONSE: Results at all doses showed hyperexcitability, tremor, dyspnea and salivation that disappeared after 3-4 days. These effects were considered transitional and therefore were not used to establish a LOEL.

OEHHA COMMENT: Page 35, second paragraph. The systemic NOEL was based on cholinesterase (ChE) activity. Thus, it is not clear why it is different from the ChE NOEL. Recommend clarifying.

DPR RESPONSE: The systemic NOEL was 3 mg/kg/day based on an increase in mortality, lung and cardiovascular effects. The ChE NOEL was less than 1 mg/kg/day, based on a significant decrease in serum ChE activity in both sexes (M: 72 - 79% in males at 9 mg/kg/day or greater; F: 19 - 38% at 9 mg/kg/day or greater) and in brain ChE activity (M: 6 - 28% at 3 mg/kg/day or greater; F: 14 - 18% at 1 mg/kg/day or greater).

OEHHA COMMENT: Page 35, second and third paragraphs. In a dermal study reported by Ebert et al. (1985b) brain ChE activity of male Wistar rats was not significantly decreased at 12 and 48 mg/kg-day. However, significant reduction in brain ChE activity was reported in male Wistar rats in a similar study at doses as low as 3 mg/kg-day (Ebert et al., 1985a). Recommend discussing the possible reason(s) for this discrepancy.

DPR RESPONSE: It was explained in the study summary why the results of the first study were not acceptable. Ebert et al. (1985a) was not acceptable according to FIFRA Guidelines since it was reported that the endosulfan administration method caused some of the deaths at all doses, dosing material was not characterized and complete histopathological examination was not performed. The subsequent study from the same laboratory was performed with revised treatment methods (see below, Ebert et al., 1985b).

Both studies were performed in the same laboratory and the Ebert et al., 1985b was supposed to be a repeat of 1985a, only with corrections to the dosing methods and differences in doses. However the dosing material was not characterized in either experiment, and there was incomplete histopathology. Therefore, these studies are considered to be supplemental.

OEHHA COMMENT: Page 36, first paragraph. It is stated that at 80 mg/kg/day, the females exhibited both a 28 percent decrease in serum ChE and a 24 percent decrease. Recommend correcting since both cannot be true.

DPR RESPONSE: Changes have been made to now read:

Males had statistically significantly decreased serum ChE at 640 mg/kg/day (-13%) and in females it was decreased at 80 mg/kg/day (-28%) and 160 mg/kg/day (-46%) when measured one day following the last dosing. Brain ChE in males was decreased 15% at 640 mg/kg/day. No ChE effects were observed in males at recovery. Females showed statistically significant decreases in serum ChE at 80 mg/kg/day (-24%) and at 160 mg/kg/day (-23%) when tested 23 days after the last dose.

OEHHA COMMENT: Page 38, last paragraph. "There was a non-dose related increase in glomerulonephritis in males at $\geq$ 0.4 mg/kg/day." This dose level does not correspond to any of the male dose levels listed in the text at the top of the paragraph or listed in Table 5. Recommend correcting.

DPR RESPONSE: Corrected

OEHHA COMMENT: Table 5. The female dose level of 0.5 mg/kg/day does not correspond to any dose level discussed in the text. Recommend correcting.

DPR RESPONSE: Corrected

OEHHA COMMENT: Table 5. Glomerulonephrosis is mentioned under footnote [d], cited in the blood vessel section of the table. It is not clear why it is mentioned here rather than under a footnote linked to the kidney section of the table. Also, recommend showing in the table the incidences of glomerulonephrosis at the different dose levels.

DPR RESPONSE: Footnote corrected and incidences of glomerulonephrosis added for all animals treated.

OEHHA COMMENT: Page 40, second paragraph. "The chronic NOEL was 0.84 (males) and 0.98 (females) mg/kg/day, based on increased mortality in the main group of females at 2.8 mg/kg/day." The publication in Food and Chemical Toxicology states that the male NOEL of 0.84 was based on decreased bodyweights in males at the next highest dose level. Recommend checking to be sure the RCD is correct.

DPR RESPONSE: Corrected as follows:

Bodyweight gain was statistically significantly decreased in males at 2.48 mg/kg/day, however the reduction was only 5% and therefore not considered to be a noteworthy effect.

OEHHA COMMENT: Page 44, second paragraph. Recommend stating the values for the increased chromosomal aberrations and abnormal metaphases in spermatocytes from dosed animals.

DPR RESPONSE: The following information was added:

Swiss male mice (8/dose) were gavaged with endosulfan (purity not stated) at 0 (distilled water), 22, 32 and 42 mg/kg/day for 5 days to examine the effect on chromosomal breakage in germ cells (Usha Rani and Reddy, 1986). Then, 60 days post-treatment, the mice were terminated and the testes were dissected out. One hundred spermatocytes were examined per mouse for structural and numerical chromosomal abnormalities at the diakinesis first metaphase stage of meiosis. To assess the significance of differences in the frequency of chromosomal abnormalities between control and treated groups the data were subjected to the Chi-squared test. Administration of endosulfan resulted in increased frequency of chromosomal aberrations and abnormal metaphases in spermatocytes (presumed to have been spermatogonia at the time of treatment) at all doses (Table 7). This effect was not observed in previous studies performed in rats (Dikshith and Datta, 1977). This study was not acceptable according to FIFRA Guidelines.

Table 7. Chromosome aberrations in Mice Induced by Different Doses of Endosulfan

Effect Observed	Dose of Endosulfan (mg/kg/day)			
	0	22	32	42
# Metaphases Scored	800	800	800	800
# Abnormal Metaphases[a]	96 (12)	106 (13.2)	148 (18.5)	172 (21.5)
# Polyploids	24 (3.0)	30 (3.8)	37 (4.6)*	52 (6.5)**
# Aneuploids(19 II)[b]	3 (0.4)	6 (0.8)*	10 (1.3)*	7 (2.1)**
# Autosomal Equivalents (19 II 1 + 1)	30 (3.8)	31 (3.9)	44 (5.5)*	46 (5.8)*
# Univalents (19 II x+y)	39 (4.9)	36 (4.5)	56 (6.8)**	51 (6.5)**
Translocations	--	3 (0.4)*	--	5 (0.6)*

a Numbers in parenthesis indicate percentage.
b II = Bivalents.
*, ** - $p < 0.05$ and 0.01, respectively.The following information was added:

Results showed after endosulfan treatment, the number of chromosome breaks was less in bone marrow and was absent in spermatogonial cells, compared to controls (% comparison). Metaphases in both bone marrow cells (11.88 at 11.6 mg/kg/day, 25.45 for control; $p < 0.001$) and spermatogonial cells (8.75 at 11.6 mg/kg/day, 11.81 for control; $p < 0.05$) were significantly decreased.

OEHHA COMMENT: Page 44, fourth paragraph. Recommend providing values for the increases in chromosomal aberrations reported in these two studies.

DPR RESPONSE: The studies in question performed with human subjects (Rupa et al., 1989a and 1989b) were actually performed with pesticide mixtures (one of which was endosulfan). No doses of any of the pesticides were stated and no aspects of the studies were performed with endosulfan alone. Therefore, since this information was not relevant to this RCD, these two studies were removed from the document.

OEHHA COMMENT: Page 44, last paragraph. "human lymphoid cells of the LAZ-007 cell line were incubated with 10^{-4}, 10^{-5} and 10^{-6}M endosulfan technical (0.41, 4.1, 41 ug/ml), respectively." The orders are reversed, recommend correcting.

DPR RESPONSE: They were corrected.

OEHHA COMMENT: Page 45, second and last paragraphs. Recommend providing values to indicate quantitatively the magnitudes of increases in these endpoints due to the test article.

DPR RESPONSE: The following was added and changed.

To assess genetic damage produced by endosulfan in germ cells of eukaryotic organisms, induction of sex-linked recessive lethals (SLRL) and sex-chromosome loss (SCL) by endosulfan was tested in *Drosophila melanogaster* (Velazquez et al., 1984). Endosulfan (50% a.i./50% kaolin in dispersing + wetting agents), dissolved in DMSO and diluted with 5% sucrose solution, was fed to first instar *Berlin-K* wild type male larvae at 0, 50 and 100 ppm until the flies had grown to adults. For adult treatment, 2-3 day old males were starved for 4 hours then fed the test solution in glass filter feeding units for 48 hours at 0, 150 and 200 ppm. The SLRL Test: 4-5 day old *Berlin-k* males treated as larvae (0, 50 and 100 ppm) and as adults (o, 150 and 200 ppm) were crossed individually with three 3-4 day old *Basc* virgin females for 3 days. The sensitivity of the germ cell stages of the males treated as adults was determined using a 3-2-2 mating scheme (broods), followed by transferring the males to fresh virgin females. The progeny of individual P males were identified so that clusters of lethals could be detected. The SCL test: 3-4 day old *Ring-X* males (treated for 24 hours at 0, 50, 100 and 200 ppm) were mass-mated in bottles to 3-4 day old *y sp* virgin females in a ratio of 2 females per male for 3 days followed by two 2-day successive broods. The F1 offspring were scored and the exceptional phenotypes were noted. Results showed a statistically significant increase in percent lethals (SLRL) in the offspring of males treated at 100 ppm as larvae (# lethals/# chromosomes tested at 0 = 7/4527; 0.15% lethals and at 100 ppm = 10/1270; 0.79%; $p < 0.05$; Kastenbaum and Bowman test). SLRL results in male germ cells exposed to endosulfan for 48 hours showed the number of lethals/number of chromosomes tested (%) were statistically significantly increased ($p < 0.05$; Kastenbaum and Bowman test) at 200 ppm in Brood 1 (3 days; 12/1034 (1.16%)), Brood 2 (14/974 (1.44%), Brood 3 (11/946 (1.16)) and in the total of all broods (37/2954 (1.25%)). SCL results with *Ring-X* adult males, treated at 0, 50, 100 and 200 ppm showed a statistical increase in F1 offspring were scored for exceptional phenotypes, or SCL. For the pooled data (3 broods) the chi-square test showed that all doses yielded a similar and significant increase of entire SCL (# XO males at 0 = 26/4416, 0.59%; 50 = 243/23142, 1.05%; 100 = 212/23536, 0.09% and 200 = 50/5858, 0.92%). Partial Y chromosome losses were not detected. There was no dose-related effect. The results suggest a more pronounced clastogenic effect in sperm, since the increase in frequency of XO exceptional offspring was significant in brood 1 at all 3 concentrations tested. Endosulfan was considered in the report to be an efficient mutagen in Drosophila. This study was not acceptable under current FIFRA Guidelines.

OEHHA COMMENT: Page 53, last paragraph. According to the data presented in Table 7 (changed to Table 8), the maternal NOEL was 0.66 mg/kg/day (based on decreased corrected bodyweight change), not 2 mg/kg/day as stated in the text and in Table 10. Recommend correcting. Also, the skeletal anomalies supporting the developmental NOEL of 2.0 mg/kg/day occurred at > 2 mg/kg/day, not ≥ 2 mg/kg/day as stated in the text. Recommend correcting.

DPR RESPONSE: The following corrections and additions were made:

The maternal NOEL of 2 mg/kg/day was based on significantly decreased mean body weight change (GD 0 to 20; -33%; corrected = – 40%), decreased absolute body weight (GD 20 = -13%; corrected = -13%) and increased clinical signs such as face rubbing (20/28) and lethargy (2/28) at 6 mg/kg/day (Table 8; formerly Table 7). While there was a 14% decrease in body weight gain (corrected) on GD 20, this effect has no toxicological significance because the corrected body weight gain is derived from at least three calculations where there is ample room for error. Additionally, there were no other statistically significant effects that were noteworthy at this dose, so this effect was not considered to be sufficient to establish a lower NOEL than 2.0 mg/kg/day. The developmental NOEL was 2 mg/kg/day, based on decreased mean fetal weights (8%), and increased growth retardation and developmental skeletal anomalies (sternebrae: small #4 and unossified) at 6.0 mg/kg/day While misaligned sternebrae number 4 was statistically significantly increased at 0.66 and 2.0 mg/kg/day (Table 8; formerly Table 7), it was not at 6.0 mg/kg/day.

Table 8. Developmental Effects Observed in Fetal Rats[a]

Observations	Treatment Level (mg/kg/day)			
	0	**0.66**	**2.0**	**6.0**
DAM EFFECTS				
Number Dams on Study at Initiation of Dosing	30	25	25	35
Number of Dams on Study Day 20 of Gestation	29	25	25	28
Number of Dams with Implants	28	23	25	27
Number of Litters with Live Fetuses	28	23	25	27
Number of Deaths	1	0	0	7
Mean Weight (g) Gravid Uterine (# Weighed)	85 (28)	85 (23)	86 (25)	78 (27)
Mean GD 20 Body Weight (g)[b] (% decrease)	428	419	416	376** (-12%)[e, f]
Mean Weight Gain (g) – GD 0 to 20[b] (% decrease)	160	155	151	108** (-33%)[f]
Corrected Body Weight (g) -- GD 20[c, b] (% decrease)	343	335	330* (-1%)[e, f]	298**[e] (-13%)[e, f]
Corrected Body Weight Gain (g) --GD 20[d]	75	70	64* (-14%)[f]	30* (-40%)[f]
FETAL EFFECTS:				
Percent Live Fetuses	97.2	96.4	91.0*	97.2
Number of Resorbed Fetuses per Litter	0.4	0.5	1.4*	0.3
Percent Resorbed Fetuses	2.8	5.2	8.5*	2.2
Mean Fetal Weight	3.8	4.0	3.9	3.5**
Mean Fetal Length (cm)	3.8	3.9	3.9	3.7*
Number of Litters with DEVELOPMENTAL ABNORMALITIES:				
Small 4th Sternebrae (% litters affected)	10 (45.5)	11 (50)	5 (20)	22 (84.6)*
Unossified 5th Sternebrae (% litters affected)	9 (41)	12 (54.5)	10 (42)	22 (84.6)**
Misaligned Sternebrae # 4 (% litters affected)	0	8 (36.4)*	8 (33)*	7 (27)*

*, ** - Significantly different from control at $p < 0.05$, 0.01, respectively.

a - Fung, 1980b

b – Mean weights (grams) were calculated only for dams that were pregnant at C-section on GD 20.

c – Weight on GD 20 minus gravid uterine weight.

d – (GD 20 body weight) - (gravid uterine weight)

e – Parentheses = % decrease in body weights or % decrease in body weight gain.

f – Percent decrease of body weights were calculated using the mean body weights only for dams pregnant at C-section.

OEHHA COMMENT: Page 66, Table 10 (currently Table 11). The inhalation LOEL should be corrected to read 0.567 rather than 0.0036.

DPR RESPONSE: Corrected

OEHHA COMMENT: Page 66, second paragraph. Here the decision is made to use the NOEL from the developmental study in rabbits (0.7 mg/kg/day) to "calculate margins of exposure for potential acute single-day human exposures to endosulfan." OEHHA agrees that this NOEL should be used for oral exposures in the human, but disagrees with using it for short-term inhalation exposures, since the inhalation route is much more sensitive than the oral route (see Table 11). Rather, OEHHA recommends using the subchronic inhalation study in the rat (NOEL = 0.194 mg/kg/day) for short-term human exposures via inhalation.

DPR RESPONSE: This entire section was changed in order to use the acceptable inhalation study for acute inhalation NOEL.

OEHHA COMMENT: Page 67, fourth paragraph. "There were no FIFRA Guideline acceptable studies for subchronic dermal exposure." Recommend correcting, since two such studies are available (discussed on pages 35-36 of the RCD). Since most worker exposure is via the dermal route, this also raises the issue of why Seasonal Average Daily Dosage (SADD) MOEs (Tables 35-37; currently Tables 36-38) were calculated using a subchronic oral NOEL, rather than a NOEL from one of these subchronic dermal studies. Recommend providing justification for using a NOEL from an oral study to calculate the dermal MOEs.

DPR RESPONSE: This entire section was changed to reflect the suggestions and also because of new information issued by USEPA (USEPA, 2007. (Wilber, D., Reaves, E., and Recore, S., January 31, 2007). **<u>MEMORANDUM</u>: Endosulfan.** The Health Effects Division's Review of California's Endosulfan Risk Characterization Draft Document (dated 12/05/2006); Reregistration Branch II; Health Effects Division (7509P), Office of Prevention, Pesticides and Toxic Substances, United
States Environmental Protection Agency, Washington, DC.

OEHHA COMMENT: Table 12 (currently Table 13). The table and text on page 68 indicate that the dogs were dosed via capsule, but the text on page 41 and the "Summary of Toxicology Data" in the Appendix indicate that the test article was fed in the diet. Recommend correcting.

DPR RESPONSE: This was corrected.

OEHHA COMMENT: Page 69, top paragraph. Here the choice is made to use the chronic dog feeding study NOEL of 0.57 mg/kg/day in calculating the non-occupational, chronic inhalation risk. However, the inhalation route is clearly more sensitive than the oral route, as illustrated by the 6- to 10-fold lower subchronic NOEL for rats dosed via inhalation compared to via the diet (formerly Table 11; currently Table 12). Thus, as discussed above, OEHHA recommends using the subchronic rat inhalation study to estimate chronic inhalation risks to bystanders (including "ambient") and workers.

DPR RESPONSE: This entire section was changed to reflect OEHHA suggestions.

OEHHA COMMENT: Page 75, third paragraph. Recommend adding PPE to the Abbreviations list.

DPR RESPONSE: This was done.

OEHHA COMMENT: Table 18 (currently Table 19). Recommend adding footnote [g].

DPR RESPONSE: This was done.

OEHHA COMMENT: Table 19 (currently Table 20). Recommend adding footnote [f].

DPR RESPONSE: This was done.

OEHHA COMMENT: Page 82, second paragraph. Recommend adding REI and PHI to the abbreviations list.

DPR RESPONSE: That was done.

OEHHA COMMENT: Page 87, second paragraph. The U.S. EPA draft 2002 Reregistration Eligibility Decision (RED) for endosulfan calculated acceptable MOEs for acute and chronic dietary exposures. Since the draft RCD used a similar methodology for dietary exposure assessment, this is cited as justification for not performing a dietary exposure assessment using more recent pesticide residue and food consumption databases. However, the U.S. EPA selected a higher critical acute NOEL (1.5 mg/kg-day, Formerly Table 42; currently Table 43). Were the U.S. EPA to use the lower acute NOEL selected in the draft RCD (0.7 mg/kg-day), some MOEs might be unacceptable. In addition, the U.S. EPA draft 2002 RED for endosulfan used the 1989-92 CSFII food consumption database, not the most recent 1994-98 CSFII database. Therefore, OEHHA recommends not citing the U.S. EPA draft 2002 RED for endosulfan as support for the sufficiency of the RCD's dietary exposure assessment.

DPR RESPONSE: The comment at the top of page 7, first paragraph, regarding the U.S. EPA draft 2002 RED. The U.S. EPA and DPR endosulfan dietary exposure assessments used the same 1989-92 CSFII consumption database. This makes dietary comparisons between the 2 documents relevant. The 1998 DPR dietary exposure assessment used a NOEL of 0.7 mg/kg-day and the 1989-92 CSFII database, that resulted in acute MOEs of 212 or higher. It is likely that a revised U.S. EPA assessment using the lower acute DPR NOEL value would still not result in MOEs below 100. This assumption is based on the combination of decreased use of endosulfan nationally, newly cancelled or revoked tolerances, and residues derived from the USDA PDP (not DPR) monitoring program. The U.S. EPA reached a similar conclusion in a January 2007 memo (U.S. EPA, 2007). Therefore, DPR believes it is appropriate to cite the 2002 U.S. EPA document.

OEHHA COMMENT: Page 87, second paragraph. Should read Appendix C rather than Appendix D.

DPR RESPONSE: Changed.

OEHHA COMMENT: Page 87, third paragraph. It is stated that endosulfan use data from 1998 were the most recent. However, at the end of the paragraph it is stated that endosulfan use remained stable from 1992-2001. Recommend harmonizing these apparently contradictory statements.

DPR RESPONSE: The statement was changed to read: Overall, national endosulfan use remained fairly stable during the 1992-2001 period for the above commodities examined individually for individual years. The 1998 data were the most recent "multi-year" data available.

OEHHA COMMENT: Table 23 (currently Table 24). Recommend explaining what "ac=high#" means. Also recommend explaining what is meant by footnote [e].

DPR RESPONSE: Comment middle of page 7, beginning with ■Table 24.• *Ac=high#* means acute value = highest residue. This change will be made.

OEHHA COMMENT: Page 90, third paragraph. Recommend explaining what is meant by a "non-systemic pesticide."

DPR RESPONSE: Explanation added: (those that stay only on the surface of the plant),

OEHHA COMMENT: Page 91, top paragraph. Should read Table 23 (currently Table 24) instead of Table 24.

DPR RESPONSE: Changed.

OEHHA COMMENT: Table 24 (currently Table 25) compares maximum endosulfan residue values in the older DPR monitoring program to those collected by the more recent Pesticide Data Program (PDP) monitoring program. Since average pesticide residue values are used by DPR for chronic dietary exposure assessments, recommend that a similar comparison also be made in Table 24 for the average endosulfan residue values. Also recommend adding apple, potato and tomato since these are the crops treated with the highest levels of endosulfan. (page 101).

DPR RESPONSE: Comment top of page 8, 1st paragraph. Originally, both text and tabular explanation existed. Text alone was considered the optimal presentation method. Since measures of central tendency are being used to define the comparisons, it would not be appropriate to add measurements at the 95th percentile.

OEHHA COMMENT: Page 94. The last paragraph is repeated.

DPR RESPONSE: Changed.

OEHHA COMMENT: Page 101, first paragraph. "The differences between the 2 surveys' consumption rates ranged from a 63% decrease in tomato consumption by nursing infants from the 1989-92 group levels to a 71% increase in potato consumption by non-nursing infants relative to the 1989-92 rates." On the following page the increase is given as 77 percent. Recommend correcting.

DPR RESPONSE: Corrected to 71%

OEHHA COMMENT: Page 102, paragraph 5. "The percent user day rate is the ratio of actual consumers divided by per capita consumption for each community." This definition is unclear. Recommend using the definition given in Table 25 (currently Table 26) in footnote [1]. However, that footnote should be corrected to read A Percent User Day Rate.

DPR RESPONSE: The definition of user day is found in Section VI Consumption Databases of the Endosulfan Dietary Exposure Addendum

OEHHA COMMENT: Pages 101 and 102, apple, pear, potato, tomato. Recommend showing the data for mean consumption rates in a table. Also recommend adding the 95th percentile consumption rates. Also recommend stating which values are based on users only and which values are based on all members of each population subgroup (users + nonusers).

DPR RESPONSE: The mean consumption values presented in Section VI Consumption Databases represent user day (active consumers) and not *per capita* consumption. The last paragraph in Section VI Consumption Databases of the Endosulfan Dietary Exposure Addendum contains a discussion of user day versus *per capita* consumption.

OEHHA COMMENT: Page 103, top paragraph. "The Exposure-1™ program estimates the annualized average exposure for all members of a designated population subgroup (TAS, 1996b)." Recommend discussing why the chronic dietary analysis is based on the entire population of each subgroup while the acute analysis is based only on the users in each population subgroup.

DPR RESPONSE: The rationale for this process is that an alternative to conducting seasonal exposure analysis is to closely examine both the acute and chronic dietary exposures for the possibility of using them as bounding range for the seasonal exposure. In a subchronic exposure scenario, individuals in a population subgroup could potentially have higher than chronic (average) exposure depending on the consumption pattern and residues on the seasonal commodities. The overall exposure for the group is, however, expected to be closer to the chronic than acute exposure because it is highly unlikely that individuals would consume commodities containing residue levels at the highest detected residues for the entire season. On the other hand, the exposure for a shorter-term (*e.g.*, 2-week) can be closer to the acute than the chronic exposure especially if the same or similar batch of food could be consumed over this period of time.

OEHHA COMMENT: Page 104, last sentence in paragraph two. Table 27 (currently Table 28) should be corrected to read Table 26.

DPR RESPONSE: Corrected.

OEHHA COMMENT: Table 26 (currently Table 27). Recommend adding the proper units to the table: µg/kg/day.

DPR RESPONSE: Corrected.

OEHHA COMMENT: Table 27 (currently Table 28). In footnote [c] the term "24-hour TWA" is used while in the table under "Air concentration" the term "Short-term" is used. In footnote [d] the term "3-day TWA" is used while in the table under "Air concentration" the term "Long-term" is used. Recommend being consistent in the use of the terminology in order to make this table more easily understood.

WH & S Response: The footnote equation terms in Table 23 of the EAD (analogous to Table 28 in the RCD; formerly Table 27) were changed to "short-term concentration" and "long-term concentration," respectively. The equation in footnote c now is: Short-Term Absorbed Daily Dosage (mg/kg/day) = (short-term concentration) x (inhalation rate).

OEHHA COMMENT: Page 106, second paragraph. States that the data in Table 28 (currently Table 29) were for the period 1990 to 2000. However, Table 28 states that sampling was through July 1996. Recommend correcting.

WH & S RESPONSE: Table 29 in the RCD is analogous to Table 15 in the EAD. To clarify any confusion resulting from the table title and text mentioning 1996, Sheryl Beauvais changed the text as follows: Historically, endosulfan has been detected numerous times in California surface waters. Guo and Spurlock (2000) summarized historical monitoring data, reported by nine different agencies between 1990 and July 2000, for pesticides in surface water in California. Monitoring for α-endosulfan, β-endosulfan, and endosulfan sulfate was conducted between August 1990 and July 1996; no monitoring has been reported since 1996 (DPR, 2004).

Table 15's title is now: Summary of Historical Surface Water Sampling Data for Endosulfan in California Through July 2000 and footnote a in Table 15 was changed to the following: Adapted from Guo and Spurlock. (2000), which summarizes water sampling conducted between August 1990 and July 2000. However, no monitoring for endosulfan has been reported since July 1996 (DPR, 2004), nor does the database differentiate between surface water systems that are sources of drinking water and those that are not (F. Spurlock, personal communication, June 7, 2005).

OEHHA COMMENT: Page 110, first paragraph. 40/89 does not equal 55%. Also, it is not obvious to this reviewer where the values 51%, 41%, 22% and 60%, 30%, 80% come from. Recommend discussing.

DPR RESPONSE: The entire section was changed to the following:

…in more than half of all combined occupational exposure scenarios (acute, subchronic, chronic), the dietary component comprised less than 3% (49/89 = 55%) of the combined exposure (data in **bold** currently Tables 31 - 33). The majority of the combined occupational exposures where diet comprised a higher percentage (3% or greater) was observed for STADD (18/35; 51%) and AADD (16/27; 59%). SADD total occupational combined exposures with a dietary component of greater than 2% was 6/27, or less than half the number for the other scenarios. The highest percentages for dietary contribution of combined occupational exposure were re-entry scenarios where STADD was 60% (9/15), SADD was 30% (3/10) and AADD was 80% (8/10) (data in **bold** currently Table 33).

OEHHA COMMENT: Table 39 (currently Table 40). Recommend using the rat two-generation dietary study (with a NOEL of 1.18 mg/kg/day) rather than the subchronic rat inhalation study (NOEL = 0.194 mg/kg/day) for calculating the non-dietary MOEs in this table. This is because the non-dietary exposures are via the oral route, not the inhalation route.

DPR RESPONSE: This was an error and has been changed.

OEHHA COMMENT: Page 118, second paragraph. This paragraph discusses subchronic dietary MOEs but no subchronic MOEs are in Table 40 (currently Table 41). Recommend adding the subchronic MOEs to the table.

DPR RESPONSE: This information was in the text above the table.

There were, however no subchronic (seasonal) dietary exposure data for endosulfan, therefore chronic dietary exposure data were used as a default.

OEHHA COMMENT: Page 118, last paragraph. "There were no percent crop treated (%CT) adjustments used in these calculations." Footnote [d] in Table 40 (currently Table 41) contradicts this statement. Recommend correcting.

DPR RESPONSE: Changed.

OEHHA COMMENT: Page 119. Regarding the formula for calculating combined margins of exposure, recommend presenting the rationale for combining exposure dosages from the oral and inhalation routes given the lower NOEL associated with the inhalation route. Lacking a rationale for doing this, OEHHA recommends calculating separate MOEs for the two routes, and then combining the results as performed in the DPR document "Methyl Bromide RCD Volume III Aggregate Exposure" dated October 24, 2002.

DPR RESPONSE: OEHHA recommendations were followed. When two or more routes were used, an aggregate exposure was calculated. This impacted scenarios where dermal, inhalation and dietary and where inhalation and dietary routes were combined (aggregate exposure: currently Tables: 36, 37, and 39) as performed in DPR document "Methyl Bromide RCD Volume III Aggregate Exposure" dated October 24, 2002. The calculations were included in the RISK CHARACTERIZATION section of V. RISK APPRAISAL and within the tables.

OEHHA COMMENT: Table 40 (currently Table 41). The acute child MOE of 212 and the acute infant MOE of 220 are relatively close to 100. This suggests that re-analysis using the more recent pesticide residue data and food consumption data is warranted. Same comment for Bystander Infants with a combined MOE of 158 in Table 38.

DPR RESPONSE: Comment top of page 8, 2nd paragraph. The acute dietary MOEs are all 212 or higher. The default threshold MOE when a NOEL is derived from an animal study is 100. The acute MOEs range between 2.12 - 5.5 fold higher than the generally accepted 100. Based on this MOE range, a re-analysis is not necessary.

OEHHA COMMENT: Page 122, second paragraph. As discussed above, OEHHA recommends using the rat subchronic inhalation study for inhalation exposures, including acute. Given that the rat subchronic inhalation LOEL was 10-fold lower than the rat subchronic oral LOEL (0.3873 versus 3.85), we believe the use of an acute oral NOEL for acute inhalation exposures would underestimate the risk. The more health-protective approach is to use the subchronic inhalation NOEL.

DPR RESPONSE: The acceptable rat subchronic inhalation study was used for acute, subchronic and chronic inhalation exposures as suggested (with an adjustment factor for chronic).

OEHHA COMMENT: Page 141, last paragraph. It is not clear from this paragraph whether the dietary risk discussed here is based on a dietary assessment as shown in Table 40 (currently Table 41), or a tolerance assessment as shown in Table 43 (currently Table 44). Recommend clarifying.

DPR RESPONSE: The dietary risk discussed refers to the information in Table 43. The following was added: The dietary risk is determined after examining MOEs for individual commodities as shown in Table 43.

OEHHA COMMENT: Page 148, second paragraph. "The resulting equivalent acute human inhalation NOEL was 0.7 mg/kg assuming a default respiratory rate of 0.59 m^3/kg/day for children." Should be corrected to read 1.2 mg/kg rather than 0.7 mg/kg.

DPR RESPONSE: Corrected.

OEHHA COMMENT: Pages 148-149. As stated above, OEHHA recommends using the subchronic rat inhalation study result for calculating all inhalation MOEs, including acute, subchronic and chronic.

DPR RESPONSE: Suggestion followed.

OEHHA COMMENT: Page 148, second paragraph. Should be corrected to read rabbit developmental study rather than rabbit reproduction study.

DPR RESPONSE: Corrected.

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Again, thank you for reviewing this document and we hope that our corrections are along the lines of your recommendations. If there are further questions, comments or suggestions, please contact Dr. Marilyn Silva (916-324-3482)(primary reviewer), or Dr. Joyce Gee (916-324-3465).

Mary-Ann Warmerdam
Director

Arnold Schwarzenegger
Governor

DATE: May 25, 2007

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FROM: Marilyn Silva, Ph.D., D.A.B.T., Toxicologist
Medical Toxicology Branch,
Department of Pesticide Regulation,
California Environmental Protection Agency

VIA: Joyce Gee, PhD., Senior Toxicologist,
Medical Toxicology Branch,
Department of Pesticide Regulation,
California Environmental Protection Agency

SUBJECT: **Endosulfan.** Department of Pesticide Regulation Response to the Endosulfan Task Force Comments on California's Endosulfan Risk Characterization Document of December 5, 2006.

This document was generated to respond to the February 18, 2007 comments generated by the Endosulfan Task Force.

Nature and Severity of Effects

Endosulfan Task Force COMMENT:

CDPR states (pages viii to ix):
Endocrine Disruption: Effects to testes and reproductive tract occurred at lower doses in prepubertal and neonatal rats than in adults following repeat exposures. The observations were from studies in the open literature (not FIFRA Guideline studies) and they occurred at doses greater than those that induced neurotoxicity. Due to these results, the US EPA considers endosulfan to be a potential endocrine disruptor. It is notable, however, that the developmental neurotoxicity study, recently received and reviewed by DPR showed no indication of neurotoxicity or endocrine disruption in rats treated with endosulfan in diet during both pre- and post-natal development. Dams, fetuses and pups showed a decrease in body weight during treatment and male pups had a slight delay (4-5%) in preputial separation at 10.8 mg/kg/day and greater.

We concur that the recent GLP DNT study (Gilmore et al. 2006) shows no potential for endocrine disruption (maternal MOAEL = 3.74 mg/kg/day; developmental neurotoxicity NOAEL = 29.8 mg/kg/day). We also note that the effects cited by EPA and CDPR from open literature (not FIFRA guideline studies) to support concern for endocrine disruption run counter to the conclusions of GLP studies. USEPA, in setting the FOPA, relied on these studies without critical analysis and, we believe, relied on these studies in error. Our comments to OEHHA (Sargent 2006) note that caution should be exercised when relying on these studies. This document is appended. In view of the new DNT study and other existing reliable data, the ETF has concluded that there is no evidence of enhanced susceptibility to younger animals, and the data do not demonstrate a potential for endocrine disruption in males or females. The assessment by EPA's FQPA Safety Factor Committee of a 10x is excessive and not justified. Concerning the overall weight-of-evidence, it is prudent to rely on acceptable guideline studies before using the open literature data that might not meet EPA's standard acceptance criteria and are often not reproducible. Therefore, we would appreciate if CDPR would not follow EPA's assessment and would take the time to reconsider using the 10x FOPA Safety Factor in its own assessment.

DPR RESPONSE: In a personal communication with USEPA, they have stated that they are in the process of re-evaluating their FQPA safety factors. DPR will defer to the USEPA decision regarding FQPA safety factors but will continue to use the 10x SF until USEPA has reported the results of the re-evaluation. Table 1 below reflects the status of the endpoint selections for DPR and USEPA.

Table 1. Comparison of critical no-observed-effect levels (NOELs) and endpoints for risk characterization between the Department of Pesticide Regulation and U.S. Environmental Protection Agency

DPR NOELs and Endpoints for Risk Characterization		
Exposure/ Species	**NOEL**	**Endpoint**
Developmental, rabbit[a] Acute Oral	0.7 mg/kg/day UF = 100[a] FQPA SF = 10	LOEL = 1.8 mg/kg; Abortions, death, convulsions, neurotoxic signs immediately after dosing, GD6 (Fung, 1981 a & b) RfD = 0.007 mg/kg/d[c]; aPAD = 0.0007 mg/kg/d[a]
21 day Inhalation, rat[b] For Acute Inhalation	0.194 mg/kg UF Interspecies= 10 UF Intraspecies= 10	Decreased body weight gain & lymphocyte counts in males; increased creatinine values in females at 0.4 mg/kg/day (LOAEL)(Hollander et al., 1984) RfC = 0.0033 mg/m^3 (0.0002 ppm)[d]
Reproduction, rat[b] Subchronic Study	1.18 mg/kg/day UF Intra/Interspecies= 100	Increased kidney and liver weights; decreased food consumption and body weights (Edwards et al., 1984)
21 day Inhalation, rat[b] Short (1-30 d); Intermediate (1-6 mo)	0.194 mg/kg/day UF Interspecies= 10 UF Intraspecies= 10	Decreased body weight gain & lymphocyte counts in males; increased creatinine values in females at 0.4 mg/kg/day (LOAEL)(Hollander et al., 1984) RfC = 0.0033 mg/m^3 (0.0002 ppm)[d]
l year dog[c] Chronic dietary Study (all populations)	0.57 mg/kg/day UF = 100 FQPA SF = 10	LOEL = 2.09 mg/kg/d; Premature deaths, neurotoxicity; dec bw gain & food consumption (Brunk, 1989);RfD = 0.0057; cPAD = 0.00057 mg/kg/d
21 day Inhalation, rat[c] For Chronic Inhalation[e]	ENEL = 0.0194 mg/kg/day UF Inter/Intraspecies= 100 UF Subchron - Chronic=10[e]	Dec body wt gain & lymphocyte counts in males; increased creatinine values in females at 0.04 mg/kg/day (ENEL)(Hollander et al., 1984) RfC = 0.00033 mg/m^3 (0.00002 ppm)[d] cPAD = 0.000033 mg/m^3
USEPA NOELs and Endpoints for Risk Characterization[f] (USEPA, 2002a)		
Acute Study Neurotoxicity, rat[a]	1.5 mg/kg/day UF = 100 FQPA = 10	LOAEL = 3 mg/kg/day; Increased convulsions in females within 8 hrs after dosing (Bury, 1997) Acute RfD = 0.015 mg/kg/day; a PAD = 0.0015 mg/kg/day (under review)
21 day Dermal, rat[b] Short-term/Subchronic	12 mg/kg/day UF Interspecies = 10 UF Intraspecies = 10	Mortality in females at 27 mg/kg/day (Ebert et al., 1985a).
21 day Inhalation, rat[b] Short-term/Subchronic	0.2 mg/kg/d (0.001 mg/L) UF Interspecies = 10 UF Intraspecies = 10	Decreased body weight gain & lymphocyte counts in males; increased creatinine values in females at 0.4 mg/kg/day; LOAEL = 0.002 mg/L (0.4 mg/kg/day) (Hollander et al., 1984)
104 week dietary, rat[c] Chronic	0.6 mg/kg/day UF = 100 FQPA = 10	Decreased body weight gain, enlarged kidneys, increased progressive glomerulonephrosis; blood vessel aneurysms (Ruckman et al., 1989). Chronic RfD = 0.006 mg/kg/day; cPAD = N/A, currently under review

a - Acute RfD = acute NOEL ÷ UF 10x (interspecies) x UF 10x (intraspecies); Population Adjusted Dose (aPAD = RfD ÷10x FQPA safety factor)

b - Subchronic, seasonal (intermediate/short-term) exposure RfD= Subchronic NOEL ÷UF (10 interspecies x 10 intraspecies); RfC = Subchronic NOEL (also used for Acute inhalation NOEL)) UF (10 interspecies x 10 intraspecies)

c - Chronic RfD = Chronic NOEL ÷ (UF 10 interspecies) x (UF 10 intraspecies)); Population Adjusted Dose (cPAD = RfD)) 10x FQPA safety factor); A 10x UF is added to the subchronic inhalation NOEL to extrapolate to obtain a chronic inhalation NOEL; ENEL = (Subchronic ÷NOEL) ÷ UF (10 interspecies x 10 intraspecies)

d - Human inhalation NOEL (mg/m^3) = animal inhalation NOEL (mg/kg/day)) respiratory $rate_{human}$ (m^3/kg) NOTE: The respiratory rate used for humans was for children (0.59 m^3/kg) who are considered to be the highest risk group; RfC (mg/m^3) = human inhalation NOEL (mg/m^3) ÷(UF 10 interspecies x UF 10 intraspecies); RfC (ppm) = RfC (mg/m^3) x (M. Vol (@ 25°C))(M.Wt. (406.9g)); Population Adjusted Dose (cPAD = RfD) 10x FQPA safety factor)

e - RfC = (Subchronic NOEL) 10 extrapolation factor)) UF (10 interspecies x 10 intraspecies)

f – The endpoints, definitive studies and critical NOELs are those published in the REREGISTRATION ELIGIBILITY DOCUMENT (USEPA, 2002). USEPA is currently re-evaluating some of their endpoints and when DPR receives the updated information it will be included in the RCD.

Note: See Section VII. REFERENCE DOSES/CONCENTRATION

Reported Illnesses (page 3 to 5)

Endosulfan Task Force COMMENT:

CDPR states (page 4, Table 1):
Illnesses Reported in California Associated with Endosulfan Exposure, 1992-2003): summarizes types of symptoms reported in association with endosulfan exposure. Of the seven illnesses and injuries attributed solely to endosulfan (1992 - 2003), one occurred as the result of exposure to field residues, three resulted from handling processes (mix/load, apply), two resulted from drift, and one followed a nonspecified exposure. Of the 55 illnesses resulting from exposure to endosulfan in combination with other pesticides, 42 occurred as the result of exposure to residue, six occurred during the application process (mix/load, apply, flag), and seven occurred as the result of drift exposure.

For illnesses where endosulfan was the sole pesticide involved, systemic effects were observed in four cases (two of which also had skin and eye involvement), while skin and eye effects occurred in three cases. In cases where endosulfan was used or encountered along with other pesticides, 27 people developed systemic symptoms (some also involved skin and eye effects), while 28 involved only skin and eye effects.

These data clearly demonstrate that the frequency of endosulfan related incidents is relatively low and the severity of the effects is minor (no hospitalization). This was also demonstrated by EPA's review (USEPA 2002), where among all the pesticide related illness reports for each active ingredient, endosulfan ranked 61st in California as a cause of systemic poisoning (California PISP 1982 - 1996), and nationwide endosulfan ranked as 65th (NPTN 1984 - 1991). Most of these incidents were related to worker field activities coming in substantial contact with foliage during harvesting, less from handling the product or spray drift exposure. However, the new mitigation measures (e.g. RUP statement, lower rates, additional PPE, extended REI and PHI, "closed mixing/loading system", "enclosed cab") that took effect after the RED was issued in 2002, should further reduce the risk of endosulfan regarding any potential poisoning cases or incidents.

<u>Key toxicological endpoints and NOAELs established for risk assessment (page 4 of 10)</u>

Acute RfD (aRfD):

CDPR states (Table 42, page 140):
CDPR notes that a developmental study in rabbits is used for establishing the acute RfD that has a NOEL of 0.7mg/kg bw/day, based on clinical signs and deaths at 1.8 mg/kg bw/day (Nye 1981).
aRfD: (0.7 mg/kg bw/day / 100 UF) = 0.007 mg/kg bw/day
aPAD: (aRfD) / 10x FQPA = 0.0007 mg/kg bw/day

USEPA cites the acute neurotoxicity study for the basis for the NOEL (1.5 mg/kg bw/day) based on increased convulsions at 3 mg/kg bw/day.

aRfD: 1.5 mg/kg bw/day + 100 UF = 0.015 mg/kg bw/day
aPAD: (aRfD) / 10x FQPA = 0.0015 mg/kg bw/day

Endosulfan Task Force COMMENT:

While all of the studies referenced by CDPR provide information regarding the acute toxicity of endosulfan, the ETF believes that the most appropriate study for establishing an acute toxicity endpoint (aRfD) for risk assessment should be the acute neurotoxicity study (Bury 1997). This guideline study is designed specifically to assess all aspects of neurotoxicity and uses testing batteries that correlate appropriate clinical signs in making a determination of neurotoxic versus other nonspecific systemic type effects. Since endosulfan is an insecticide whose main mode of action is neurotoxicity (see above), the acute neurotoxicity study evaluated the range of clinical signs of neurotoxicity at the time to peak effect from a single dose.

In addition, while the effects noted in dams in the rabbit teratology study at the higher doses should be considered in the weight-of-evidence, a single clinical observation (e.g. hyperactivity) in the absence of other evidence of toxicity is not sufficient to establish an acute neurotoxic effect level. This position is also supported in EPA's review of the endosulfan acute toxicity data:

The database included a lower NOAEL (maternal) of 0.7 mg/kg/day in the rabbit developmental toxicity study (MRID# 00094837), based on salivation, convulsions, rapid breathing, and hyperactivity seen at 1.8 mg/kg/day. The Committee, however, decided not to use this NOAEL for this (acute) scenario because the clinical signs in the dams were seen on day 10 of gestation (i.e., after 4 treatments), whereas in the acute neurotoxicity study, convulsions were seen 8 hours after a single oral dose, thus making this endpoint more appropriate for this risk assessment" (US EPA 2000).

Based on this information, the ETF recommends in agreement with EPA that the acute neurotoxicity study should be used to establish the acute toxicity effect level for human health risk assessment (NOAEL of 1.5 mg/kg/day). In addition the ETF request removal of the 10X FOPA Safety factor based on the results from the DNT study (see above), and request to change the aPAD to 0.015 mg/kg bw/day.

In contrast, CPDR does note that the rabbit developmental study was a repeat dose study but supported their selection of 0.07 mg/kg bw/day as the appropriate NOEL since effects were noted after one dose.

DPR RESPONSE: DPR selected the developmental neurotoxicity study for the critical oral NOEL because there were no major deficiencies and it provided the lowest acute oral NOEL. Similar effects were observed in 2 rangefinding studies also performed in pregnant New Zealand rabbits (Fung, 1981a, b). In these studies the LOELs were 1.0 mg/kg/day, based on neurotoxicity and deaths beginning day 8 of gestation (treatment day 2). The other studies described in the RCD (summarized in Table 2, below), showed that female rats are more sensitive to acute oral endosulfan treatment than are males and that pregnant female rabbits are more sensitive to endosulfan than are both non-pregnant and pregnant rats. Although the rabbit developmental study involved multiple dosing, rather than a single acute oral dose of endosulfan, the neurotoxic effects were seen on the first day of treatment and were therefore acute oral effects. Therefore, this study, with a critical NOEL of 0.7 mg/kg, was selected as the definitive study for evaluating acute dietary exposure and to calculate the MOE for potential acute single-day (non-inhalation) human exposures to endosulfan. While the acute neurotoxicity in rat study was designed specifically to test for acute neurotoxicity, the rabbit proved to be the more sensitive species.

Table 2. The Acute Effects of Endosulfan and the NOELs and LOELs

Species	**Exposure**	**Effect**	**NOEL mg/kg**	**LOEL mg/kg**	**Ref[a]**
ORAL					
Rat[b] Male	Single Gavage	Death, clinical signs, irritation of stomach and small intestine; congestion of kidneys, lungs and adrenals, LD_{50} = 48 mg/kg	--	31.6	1
Rat[b] Female	Single Gavage	Death, clinical signs, reddening of small intestine, LD_{50} = 10 mg/kg	--	6.3	2
Rat M/F	Single Gavage	Death, clinical signs, neurotoxicity	M 12.5 F 1.5	M 25 F 3.0	3*
Rat Female	8 Days Gavage	Dams: Death, decreased body weight, clinical signs Fetuses: Increased anomalies and malformations	2.0	6.0 HDT	4
Rabbit Female	**12 Days Gavage**	**Death, clinical signs beginning the first day of treatment**	**0.7**	**1.8 HDT**	**5***
DERMAL					
Rabbit[b, c]	Single Dermal	Death, erythema, atonia, slight desquamation, hemorrhagic lungs, granular livers, irritation of large intestine, congested kidneys (clinical signs not described) LD_{50} = 359 mg/kg	--	46.4	6
INHALATION					
Rat[b, d] M/F	Single 4 Hour Nose Only	Death, clinical signs	--	0.567	7

a - 1. Scholz and Weigand, 1971a; 2. Scholz and Weigand, 1971b; 3. Bury, 1997; 4. Fung, 1980b; 5. Nye, 1981; 6. Elsea, 1957; 7. Hollander and Weigand,1983
b - LD_{50}/LC_{50} study
c - Gender unspecified
d – For information on this study, see RCD Subchronic Inhalation
* - Designates studies that are acceptable, according to FIFRA Guidelines.HDT = Highest Dose Tested
Bold = Definitive test for the critical NOEL.

Subchronic, seasonal (intermediate) occupational exposure

Endosulfan Task Force COMMENT:

CDPR states (Table 42, pages 66 and 140):
Two NOELs are noted: 1.18 mg/kg bw/day based on increased kidney and liver weights and decreased food intake and body weights in a rat reproduction (oral) study (Edwards et al., 1984) and 0.2 mg/kg bw/day based on decreased body weight gain and lymphocyte counts in males and

increased creatinine values in females at 0.4 mg/kg bw/day at 0.4 mg/kg bw/day in a 21-day rat inhalation study (Hollander and Weigand 1984).

Subchronic RfD $_{oral}$ 1.18 mg/kg bw/day /100 UF = 0.018 mg/kg bw/day

USEPA cites two NOELs: 12.0 mg/kg bw/day, based on mortality in females at 27 mg/kg bw/day in a repeat dose 21-day dermal study in rats (Ebert et al., 1985) and 0.2 mg/kg bw/day, as noted above (Hollander et al., 1984) for short- and intermediate-term inhalation.

Sub chronic RfD_{dermal} 12 mg/kg bw/day / 100 UF = 0.12 mg/kg bw/day
Subchronic $RfD_{inhalation}$: 0.2 mg/kg bw/day / 100 UF = 0.002 mg/kg bw/day

We believe that occupational risk assessments based on NOAELs from appropriate dermal toxicity studies, rather than based on oral toxicity studies that are then adjusted by an estimated dermal penetration factor in this case 47.3%, are more accurate and appropriate to use. For endosulfan occupational risks, an appropriate dermal study in rabbits is available and has been used by the USEPA for their occupational risk assessments. Therefore, the ETF asks that DPR revise their occupational risk assessments to change the NOAEL basis from the oral to the dermal study.

DPR RESPONSE: According to the current revision of USEPA'S risk assessment document for endosulfan, the following studies are being used for dermal short term and long term exposure estimates (see Table 1 of this document; USEPA, 2002):

Dermal Short-term and Subchronic Studies--Dermal Rat: NOEL = 12 mg/kg/day (45% Dermal absorption), Ebert et al., 1985.
Occupational LOC/MOE = 100

DPR did not establish a subchronic dermal endpoint, since there were no acceptable studies.

For seasonal occupational (dermal), subchronic swimmer in surface water and combined (Total Occupational + Dietary) MOE estimates, DPR used a rat reproduction dietary study (Edwards et al., 1984) with a NOEL of 1.18 mg/kg/day based on increased kidney weights, decreased food consumption, and decreased body weights for MOE estimates. A dermal absorption of 47.3% (Craine, 1988) from a dermal rat study was used in the DPR exposure assessment (Beauvais, 2006). The USEPA did not establish a subchronic dietary endpoint study.

Subchronic inhalation toxicity endpoint

Endosulfan Task Force COMMENT:

CDPR states (page 67):
"... This study was therefore selected as the definitive study (Hollander et al. 1984) for the critical NOEL of 0.194 mg/kg/day…"

The ETF does not believe that an inhalation endpoint is the most appropriate for human health risk assessment. In regard to the determination of a subchronic inhalation toxicity endpoint for risk assessment, the ETF does not concur with CDPR's selection of the NOEL of 0.194 mg/kg/day from the 21-day inhalation study (Hollander et aI., 1984, MRID# 00147183). EPA selected a NOEL of 0.24 mg/kg/day from the study (USEPA 2000). In this study, the low concentration (0.0024 mg/L) and high concentration (0.0065 mg/L) groups received airborne particles that were primarily below 6 µm in diameter. Roughly 92 to 98 percent of the particles were below 6 µm in diameter in the case of the low concentration group and approximately 88 to 90 percent of the particles delivered to the test animals in the high concentration group were less than 6 µm in diameter. The results of this study may not be directly applicable to assessing the risk associated with worker exposures because workers are exposed primarily to a size range of larger diameter particles in the field due to use of standard application equipment. By comparison, standard agricultural spray equipment, such as airblast, ground boom and aerial spray rigs, generate relatively coarse aerosol sizes. More than 90 percent of the mass of particulates generated by agricultural application equipment are greater than 30µm in diameter (Ross et al. 2001). Thus, no more than 10 percent of the total applied mass consists of aerosols that would be in the respirable range (i.e., less than 10µm in diameter). Most of the aerosols contacting the breathing zone of the applicator would be removed by the specified respirator with an approved pre-filter that is required for all mixer/loaders and applicators of endosulfan WP and EC formulations where an enclosed cab is not involved. Particles of these larger diameters generated in the field that could possibly by-pass the respirator (e.g., in cases where less than ideal fit is obtained) would be expected to become inhaled and impacted in the upper respiratory tract, after which they would be rapidly cleared and swallowed, thus, becoming an oral dose. For this reason, Ross et al., (2001) recommends that in assessing pesticide handler inhalation risk, the inhalation exposure estimate should be compared to an oral NOAEL. Therefore, it seems to be more appropriate to use, the NOAEL of 1.5 mg/kg/day from the acute oral neurotoxicity study (Bury 1997) for assessing short-term inhalation exposures to handlers (i.e., mixer/loaders, applicators, flaggers; see also (Whitmyer 2001).

We would like to reiterate that since the RED has been published, new mitigation measures are being implemented (RUP classification, reduced use rates, extended REls and PHis, additional PPEs, "closed mixing/loading system", "enclosed cab"). We request that CDPR would consider these changes and revise the endosulfan risk assessment accordingly.

DPR RESPONSE: USEPA uses the same NOEL for the rat inhalation study, as does DPR (see Table 1, above).

In a seminar presented by Ayaad Assaad, John C. Redden, and John E. Whalen entitled "Inhalation Toxicology and Risk Assessment" a slide was presented that specifically addressed the issue of inhaled particle size. They ask: "Why do we require MMAD of 1-4 µm in rodent studies when we know humans are exposed to much larger particles?"

The slide contains 4 statements in response to this question. These are paraphrased below:

1) Rodents are obligate nose breathers, and their nasal airways are very efficient at removing inhaled particles.

2) Because of this, a range of particles exists in which particles are small enough to reach the human lung but are captured in the rodent nose.

3) To simulate human exposure, rodents are exposed to MMAD 1-4 μm particles to assure that particles will reach their lungs.

4) Sprayed particles, e.g. from a crop duster, may be 100-500 μm when sprayed, but due to evaporation their sizes decrease to the range of inhalable and respirable particles.

In addition to this, it is the policy of DPR to use inhalation studies when available and FIFRA Guideline acceptable for estimates of exposure (with the standard conversion factors). In light of the fact that endosulfan might be considered to be a toxic air contaminant, the availability of an acceptable inhalation study is useful.

<u>Chronic RfD (cRfD):</u>

Endosulfan Task Force COMMENT:

CDPR states (Table 42, page 140): The NOAEL of 0.57 mg/kg bw/day is based on premature deaths and neurotoxic effects (e.g, violent contractions of the upper abdomen) in a one year dog study (oral by capsule) at 2.09 mg/kg bw/day (Brunk 1989).

cRfD: 0.0057 (NOEL /100 UF); cPAD: 0.00057 (cRfD /FQPA 10x UF)

USEPA uses a NOAEL of 0.6 mg/kg bw/day based on a chronic rat study based on decreased body weight, enlarged kidneys in females, increased progressive glomerulonephritis in females and blood vessel aneurysms in males (Ruckman et al. 1989).

cRfD: 0.006 mg/kg bw/day; cPAD: 0.0006mg/kg bw/day

We do not concur with the respective chronic RfDs used by CPDR and USEPA by means of the additional 10X FOPA safety factor, since the new DNT study demonstrated that there is no evidence of enhanced susceptibility to younger animals, and the data do not demonstrate a potential for endocrine disruption in males or females. Therefore, the appropriate cPAD should be 0.006 mg/kg bw/day, instead of 0.0006 mg/kg/day.

<u>Uncertainty Factors:</u>

DPR states: The uncertainty factor for occupational risk is 100, generally, but 1000 for infants and children (Risk Characterization, page 132). Generally an MOE of at least 100 is considered sufficiently protective of human health when the NOEL for an adverse systemic effect is derived from an animal study. This MOE allows for the possibility of humans being 10 times more sensitive than animals and for a 10-fold variation in sensitivity between the lower range of the normal distribution in the overall population and the sensitive subgroup (Dourson et al., 2002). However, when considering endosulfan exposure for the general public, specifically infants exposed in ambient air or as bystanders, the above MOE of 100 is insufficient. For infants and children exposed in ambient air or as bystanders, MOEs need to be at least 1000-fold or greater. MOEs of less than 1000 for these scenarios result in the consideration of listing endosulfan as a toxic air contaminant (TAC, 2001) based on acute, subchronic and chronic toxicity.

ETF COMMENT: We believe that a MOE of 100, based on a 100-fold uncertainty factor, is sufficient for protection of the population, including infants and children. JMPR in their draft evaluation of endosulfan also use a 100-fold uncertainty factor (McGregor 1998).

The open literature studies that, in large measure, support EPA's 10-fold FQPA uncertainty factor are non-GLP, have issues associated with them, and have been rebutted (Sargent 2006). In addition, the DNT study has been completed, does not show neurotoxic or endocrine effects (as reviewed by cPDR) and fills the data gap that was cited by USEPA as supporting the 10x FOPA uncertainty factor.

DPR RESPONSE: Currently USEPA is revising their FQPA safety factor for their chronic exposure (oral) (see Table 1, above). DPR will continue to use the 10x safety factor until USEPA has concluded the re-evaluation of its FQPA decision.

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M E M O R A N D U M

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FROM: Sheryl Beauvais
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DATE: June 29, 2007

SUBJECT: RESPONSE TO OEHHA COMMENTS ON ENDOSULFAN RISK CHARACTERIZATION DOCUMENT

The Office of Environmental Health Hazard Assessment (OEHHA) sent comments, dated March 1, 2007, on the Department of Pesticide Regulation's (DPR's) revised final draft Risk Characterization Document (RCD) for endosulfan, dated December 5, 2006. Although the draft exposure assessment document (EAD) was attached to the RCD, OEHHA did not specifically comment on the EAD. However, some of the comments about the RCD relate specifically to information in the EAD. Responses to those comments are given below. All of these changes have been communicated to the risk assessor for incorporation into the RCD.

(OEHHA memo page 3): *Page four, second paragraph. "Of the 55 illnesses resulting from exposure to endosulfan in combination with other pesticides, 42 occurred as the result of exposure to residue,..." Recommend clarifying whether these were field residues, or some other type of residue.*

Response: The word "field" was inadvertently omitted. I've added it ("field residues on treated crops"). Also, inclusion of illness reports from 2004 added a single illness associated with endosulfan; this illness was also reported by a fieldworker exposed to field residues. The first three paragraphs of the Reported Illnesses have been changed as follows:

> Reports of illness and injury with definite, probable, or possible exposure to pesticide products are recorded in a database maintained by the Pesticide Illness Surveillance Program (PISP) at DPR. The PISP database contains information about the nature of the pesticide exposure and the subsequent illness or injury. In California between 1992 and 2004, 63 illnesses were reported to the Pesticide Illness Surveillance Program that suggested the involvement of endosulfan, alone or in combination with other pesticides (Verder-Carlos, 2006). Of the 63 illnesses, 61 resulted from agricultural applications and just two from non-agricultural applications. Five agriculturally-related and both of the non-agriculturally-related

illnesses and injuries were attributed solely to endosulfan; the other 56 reports were associated with endosulfan in combination with other pesticides.

Of the seven illnesses and injuries attributed solely to endosulfan, one occurred as the result of exposure to field residues, three resulted from handling processes (mix/load, apply), two resulted from drift, and one followed a non-specified exposure. Of the 56 illnesses resulting from exposure to endosulfan in combination with other pesticides, 43 occurred as the result of exposure to field residues on treated crops, six occurred during the application process (mix/load, apply, flag), and seven occurred as the result of drift exposure.

Table 2 summarizes types of symptoms reported in association with endosulfan exposure. The majority of illnesses involved skin and eye effects, such as irritation and rashes. Several incidents involved more than one worker. None of the incidents resulting in multiple exposures involved endosulfan as the only pesticide. Of the 44 field worker illnesses and injuries, 31 (70%) occurred while harvesting cucurbits (melons, cucumbers), and seven (16%) occurred while working in grapes. The remaining six (14%) occurred in various other crops.

(OEHHA memo page 3): *Page four, last paragraph. If available, recommend stating the length of exposure rather than "prolonged."*

Response: I agree, and I changed the paragraph as follows:

In the southeastern U.S., two incidents were reported in which mixer/loader/applicators (M/L/As) pouring endosulfan without proper protective equipment experienced serious illnesses (Brandt *et al*., 2001). In both cases, endosulfan splashed onto skin and clothing during mixing and loading; in the second case, drift during the application, enough that his clothes “appeared soaked,” was witnessed. Both individuals proceeded with the applications without washing skin or changing the contaminated clothing. Exposure durations were estimated at 4 - 5 hours. Evidence suggested that these exposures resulted in long-term neurological damage in one case, and in death in the other case.

(OEHHA memo page 4): *Page 16, third paragraph. It is not clear why the percent total absorption (47.3 percent) was calculated using the percent absorption at the two lowest dose levels, rather than just the percent absorption at the lowest dose level (the lowest dose level showed the greatest absorption at 24 hours). Since the value of 47.3 percent is used by the Worker Health and Safety Branch to calculate occupational exposures, we recommend this be explained.*

Response: The mean 168-hour absorption of the two lowest doses was used, rather than the absorption of the lowest dose, because at 168 hours the greatest absorption was associated with the mid-level dose, not the lowest dose - but the percent absorption was nearly the same for both doses (see Table 6 in the EAD). Although greater penetration was documented in the lowest dose than in the other doses at 24 hours, at that point there were extensive bound skin residues. Had the 24-hour low-dose results been used, all of the bound skin residues would have been included in the absorbed dose estimate (because we anticipate that some portion would be absorbed), resulting in an estimated 63.5% dermal absorption value (22.1% penetrated + 41.4% bound to skin). As we have data at 7 days (168 hours) showing that the total residues that were penetrated and bound to skin is just under 50% (44.8% + 1.7% = 46.5%), using the 24-hour value would give an inappropriate overestimate of dermal absorption. To clarify in the EAD, I revised the text before Table 6 as follows:

> Craine (1988) reported that amounts of ^{14}C-endosulfan recovered from the application site decreased over time, while amounts of residues in excreta increased. These trends suggest that residues bound to skin are bioavailable. For example, at 24 hrs in the low dose animals, the residues in the skin represented 41.4% of the applied dose; residues declined to 23.8% and 7.0%, respectively, at the 48-and 72-hr sacrifice time periods. Similar declines in bound skin residues occurred at the two higher treatment levels.
>
> A portion of the bound skin residues recovered in any dermal absorption study are expected to be absorbed; as the amount that will be absorbed is unknown, standard practice is to include bound skin residues in estimates of absorbed dose (U.S. EPA, 1998). The results from 168 hours post-dose suggest that much of the residues in the skin at 24 hours were not absorbed. Because of the large amount of residue bound to skin at 24 hours, dermal absorption can be more accurately estimated using data from 168 hours post-dose (Table 6). DPR selected the mean dermal penetration of the two lowest doses (47.3%) to estimate absorbed dosages, as the lowest doses approximate levels of endosulfan exposure experienced by handlers and fieldworkers. Total recoveries of administered doses averaged above 90%, precluding any need to adjust the estimated dermal absorption for absorbed dose recovery.

(OEHHA memo page 8): *Table 27. In footnote c the term "24-hour TWA" is used while in the table under "Air concentration" the term "Short-term" is used. In footnote d the term "3-day TWA" is used while in the table under "Air concentration" the term "Long-term" is used. Recommend being consistent in the use of the terminology in order to make this table more easily understood.*

Response: I changed the footnote equation terms in Table 23 in the EAD (analogous to Table 27 in the RCD) to "short-term concentration" and "long-term concentration," respectively. The equation in footnote c now is: Short-Term Absorbed Daily Dosage (mg/kg/day) = (short-term concentration) x (inhalation rate).

(OEHHA memo page 8): *Page 106, second paragraph. States that the data in Table 28 were for the period 1990 to 2000. However, Table 28 states that sampling was through July 1996. Recommend correcting.*

Response: Table 28 in the RCD is analogous to Table 15 in the EAD. To clarify any confusion resulting from having the table title and text mention 1996, I changed the text as follows: "Historically, endosulfan has been detected numerous times in California surface waters. Guo and Spurlock (2000) summarized historical monitoring data, reported by nine different agencies between 1990 and July 2000, for pesticides in surface water in California. Monitoring for α-endosulfan, β-endosulfan, and endosulfan sulfate was conducted between August 1990 and July 1996; no monitoring has been reported since 1996 (DPR, 2004)."

Table 15's title is now, "Summary of Historical Surface Water Sampling Data for Endosulfan in California Through July 2000," and footnote a in Table 15 was changed to the following:

> Adapted from Guo and Spurlock (2000), which summarizes water sampling conducted between August 1990 and July 2000. However, no monitoring for endosulfan has been reported since July 1996 (DPR, 2004), nor does the database differentiate between surface water systems that are sources of drinking water and those that are not (F. Spurlock, personal communication, June 7, 2005).

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